



Immugen

Pharmaceuticals, INC.

O:305.666.4093
F:305.669.4750
C:305.321.7458
crt@immugen.com

May 22, 2004

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Attn. Brian S. Kwon

Re: Application No. 10/738,457 and 09/967,353

Dear Mr. Kwon,

As you may or may not know, I am no longer represented by Leydig, Voit and Mayer and must respond to any office actions on my own until I can engage the services of another law firm or continue on my own.

I have enclosed a copy of a letter which I submitted today to the Commissioner for Patents which accompanies the Information Disclosure Statement pertaining to 10/738,457. I had raised the issue of the outstanding Office Action in connection with the parent application 09/967,353 which according to a letter dated December 17, 2003 carried a final response date of January 16, 2004. Although the letter goes on to state that the subject matter will be further prosecuted by way of the continuation application, I need to clarify the status of the application since I do not want to abandon it. Also, at what time is it possible to amend the title to the patent application since I understand that you are not allowing the claim for platelet aggregation? Of course, if I can argue successfully for the claim, then I would not have to change the title.

Thank you for your attention to this matter.

Sincerely,


Craig R. Travis, M.D.



Approved for use through 06/30/2006. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

[illegible]

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Aharony D, Smith JB, Silver MJ.
Regulation of arachidonate-induced platelet aggregation by the lipoxygenase product, 12-hydroperoxyeicosatetraenoic acid.
Biochim Biophys Acta. 1982 Oct 8;718(2):193-200.

Alanko J, Riutta A, Holm P, Mucha I, Vapaatalo H, Metsa-Ketela T.
Modulation of arachidonic acid metabolism by phenols: relation to their structure and antioxidant/prooxidant properties.
Free Radic Biol Med. 1999 Jan;26(1-2):193-201.

Alanko J, Riutta A, Vapaatalo H.
Phenols inhibit prostaglandin E2 synthesis in A23187-stimulated human whole blood and modify the ratio of arachidonic acid metabolites.
Prostaglandins Leukot Essent Fatty Acids. 1995 May;52(5):299-301.

Alanko J.
Effects of phenols on eicosanoid synthesis in A23187-stimulated human whole blood.
Prostaglandins. 1993 Mar;45(3):193-201.

Alanko J, Riutta A, Mucha I, Vapaatalo H, Metsa-Ketela T.
Modulation of arachidonic acid metabolism by phenols: relation to positions of hydroxyl groups and peroxy radical scavenging properties.
Free Radic Biol Med. 1993 Jan;14(1):19-25.

Andersen NH, Eggerman TL, Harker LA, Wilson CH, De B.
On the multiplicity of platelet prostaglandin receptors. I. Evaluation of competitive antagonism by aggregometry.
Prostaglandins. 1980 May;19(5):711-35.

Barrett ML, Gordon D, Evans FJ.
Isolation from Cannabis sativa L. of cannflavin--a novel inhibitor of prostaglandin production.
Biochem Pharmacol. 1985 Jun 1;34(11):2019-24.

Barry OP, Kazanietz MG, Pratico D, FitzGerald GA.
Arachidonic acid in platelet microparticles up-regulates cyclooxygenase-2-dependent prostaglandin formation via a protein kinase C/mitogen-activated protein kinase-dependent pathway.
J Biol Chem. 1999 Mar 12;274(11):7545-56.

Barry OP, Pratico D, Savani RC, FitzGerald GA.
Modulation of monocyte-endothelial cell interactions by platelet microparticles.
J Clin Invest. 1998 Jul 1;102(1):136-44.

Belton O, Byrne D, Kearney D, Leahy A, Fitzgerald DJ.
Cyclooxygenase-1 and -2-dependent prostacyclin formation in patients with atherosclerosis.
Circulation. 2000 Aug 22;102(8):840-5.

Bertele V, De Gaetano G.
Potentiation by dazoxiben, a thromboxane synthetase inhibitor, of platelet aggregation inhibitory activity of a thromboxane receptor antagonist and of prostacyclin.
Eur J Pharmacol. 1982 Dec 3;85(3-4):331-3.

Bills TK, Smith JB, Silver MJ.
Intracellular regulation of the metabolism of arachidonic acid in human platelets.
Thromb Haemost. 1978 Oct 31;40(2):219-23. Review.

Bing RJ, Yamamoto T, Yamamoto M, Kakar R, Cohen A.
New look at myocardial infarction: toward a better aspirin.
Cardiovasc Res. 1999 Jul;43(1):25-31. Review.

Born GV.
Aggregation of blood platelets by adenosine diphosphate and its reversal.
Nauchni Tr Vissh Med Inst Sofia. 1962 Jun 9;194:927-9.

Bornheim LM, Grillo MP.
Characterization of cytochrome P450 3A inactivation by cannabidiol: possible involvement of cannabidiol-hydroxyquinone as a P450 inactivator. Chem Res Toxicol. 1998 Oct;11(10):1209-16.

Burstein S, Raz A.
Inhibition of prostaglandin E2 biosynthesis by delta 1-tetrahydrocannabinol.
Prostaglandins. 1972 Nov;2(5):369-74.

Burstein S, Levin E, Varanelli C.
Prostaglandins and cannabis. II. Inhibition of biosynthesis by the naturally occurring cannabinoids. Biochem Pharmacol. 1973 Nov 15;22(22):2905-10.

Burstein S, Varanelli C, Slade LT.
Prostaglandins and cannabis-III. Inhibition of biosynthesis by essential oil components of marijuana. Biochem Pharmacol. 1975 May 1;24(9):1053-4.

Burstein SH, Audette CA, Doyle SA, Hull K, Hunter SA, Latham V.
Antagonism to the actions of platelet activating factor by a nonpsychoactive cannabinoid.
J Pharmacol Exp Ther. 1989 Nov;251(2):531-5.

Camacho M, Vila L.

Transcellular formation of thromboxane A₂ in mixed incubations of endothelial cells and aspirin-treated platelets strongly depends on the prostaglandin I-synthase activity. *Thromb Res.* 2000 Jul 15;99(2):155-64.

Camacho M, Lopez-Belmonte J, Vila L.

Rate of vasoconstrictor prostanoids released by endothelial cells depends on cyclooxygenase-2 expression and prostaglandin I synthase activity. *Circ Res.* 1998 Aug 24;83(4):353-65.

Evans AT, Formukong EA, Evans FJ.

Actions of cannabis constituents on enzymes of arachidonate metabolism: anti-inflammatory potential. *Biochem Pharmacol.* 1987 Jun 15;36(12):2035-7

Evans AT, Formukong E, Evans FJ.

Activation of phospholipase A₂ by cannabinoids. Lack of correlation with CNS effects. *FEBS Lett.* 1987 Jan 26;211(2):119-22.

Evans FJ. Cannabinoids: the separation of central from peripheral effects on a structural basis. *Planta Med.* 1991 Oct;57(7):S60-7. Review.

Fiddler GI, Lumley P.

Preliminary clinical studies with thromboxane synthase inhibitors and thromboxane receptor blockers. A review.

Circulation. 1990 Jan;81(1 Suppl):I69-78; discussion I79-80. Review.

FitzGerald GA, Austin S, Egan K, Cheng Y, Pratico D.

Cyclo-oxygenase products and atherothrombosis. *Ann Med.* 2000 Dec;32 Suppl 1:21-6. Review.

FitzGerald GA, Oates JA.

Selective and nonselective inhibition of thromboxane formation.

Clin Pharmacol Ther. 1984 May;35(5):633-40.

FitzGerald GA, Brash AR, Oates JA, Pedersen AK.

Endogenous prostacyclin biosynthesis and platelet function during selective inhibition of thromboxane synthase in man.

J Clin Invest. 1983 Oct;72(4):1336-43.

FitzGerald GA, Pedersen AK, Patrono C.

Analysis of prostacyclin and thromboxane biosynthesis in cardiovascular disease. *Circulation.* 1983 Jun;67(6):1174-7.

Formukong EA, Evans AT, Evans FJ.

The inhibitory effects of cannabinoids, the active constituents of *Cannabis sativa* L. on human and rabbit platelet aggregation.

J Pharm Pharmacol. 1989 Oct;41(10):705-9.

- Formukong EA, Evans AT, Evans FJ.
The inhibitory effects of cannabinoids, the active constituents of *Cannabis sativa* L. on human and rabbit platelet aggregation.
J Pharm Pharmacol. 1989 Oct;41(10):705-9.
- Formukong EA, Evans AT, Evans FJ.
Analgesic and antiinflammatory activity of constituents of *Cannabis sativa* L. Inflammation. 1988 Aug;12(4):361-71.
- Formukong EA, Evans AT, Evans FJ.
The Medicinal Uses of Cannabis and its Constituents Phytotherapy Research, 1989 Vol. 3, No. 6: 219-231.
- Fratantoni JC, Poindexter BJ.
Characterization of the platelet response to exogenous arachidonic acid. Thromb Res. 1981 Apr 1-15;22(1-2):157-66. .
- Hsuanyu Y, Dunford HB.
Prostaglandin H synthase kinetics. The effect of substituted phenols on cyclooxygenase activity and the substituent effect on phenolic peroxidatic activity.
J Biol Chem. 1992 Sep 5;267(25):17649-57.
- James MJ, Penglis PS, Caughey GE, Demasi M, Cleland LG.
Eicosanoid production by human monocytes: does COX-2 contribute to a self-limiting inflammatory response?
Inflamm Res. 2001 May;50(5):249-53. Review.
- Johnson M, Carey F, McMillan RM.
Alternative pathways of arachidonate metabolism: prostaglandins, thromboxane and leukotrienes.
Essays Biochem. 1983;19:40-141. Review.
- Kalofoutis A, Lekakis J, Koutselinis A.
Effects of delta 9-THC on human platelet phospholipids.
Pharmacol Biochem Behav. 1980 May;12(5):697-9.
- Kitagawa S, Ito Y, Oda Y, Kametani F.
Inhibitory effects of phenol derivatives on bovine platelet aggregation and their effects on Ca²⁺ mobilization.
Biochim Biophys Acta. 1989 Mar 28;1011(1):52-7.
- Kudo I, Murakami M.
Diverse functional coupling of prostanoid biosynthetic enzymes in various cell types.
Adv Exp Med Biol. 1999;469:29-35.

Kulmacz RJ, Lands WE.
Stoichiometry and kinetics of the interaction of prostaglandin H synthase with anti-inflammatory agents.
J Biol Chem. 1985 Oct 15;260(23):12572-8.

Libby P.
Current concepts of the pathogenesis of the acute coronary syndromes.
Circulation. 2001 Jul 17;104(3):365-72. Review. .

Libby P.
Molecular bases of the acute coronary syndromes.
Circulation. 1995 Jun 1;91(11):2844-50. Review. .

Linder BL, Goodman DS.
Studies on the mechanism of the inhibition of platelet aggregation and release induced by high levels of arachidonate.
Blood. 1982 Aug;60(2):436-45.

McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA.
Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2.
Proc Natl Acad Sci U S A. 1999 Jan 5;96(1):272-7. Erratum in: Proc Natl Acad Sci U S A 1999 May 11;96(10):5890.

Nathan I, Agam G, Mechoulam R, Dilansky A, Livne AA.
Effect of synthetic enantiomeric cannabinoids on platelet aggregation.
Can J Physiol Pharmacol. 1992 Oct;70(10):1305-8.

Nathan I, Yarom A, Dvilansky A, Lander N, Livne A.
Cannabinoids and serotonin uptake by blood platelets: evidence for multiple sites of action.
Biochem Pharmacol. 1982 Feb 1;31(3):439-41. .

Reilly M, Fitzgerald GA.
Cellular activation by thromboxane A2 and other eicosanoids.
Eur Heart J. 1993 Dec;14 Suppl K:88-93. Review.

Ross R. Atherosclerosis is an inflammatory disease.
Am Heart J. 1999 Nov;138(5 Pt 2):S419-20. Review. .

Sekiya F, Takagi J, Sasaki K, Kawajiri K, Kobayashi Y, Sato F, Saito Y.
Feedback regulation of platelet function by 12S-hydroxyeicosatetraenoic acid: inhibition of arachidonic acid liberation from phospholipids. Biochim Biophys Acta. 1990 May 1;1044(1):165-8.

Silver MJ, Smith JB, Ingerman C, Kocsis JJ.

Arachidonic acid-induced human platelet aggregation and prostaglandin formation.

Prostaglandins. 1973 Dec;4(6):863-75.

Spronck HJ, Luteijn JM, Salemink CA, Nugteren DH.

Inhibition of prostaglandin biosynthesis by derivatives of olivetol formed under pyrolysis of cannabidiol. Biochem Pharmacol. 1978 Feb 15;27(4):607-8.

Tansik RL, Namm DH, White HL.

Synthesis of prostaglandin 6-keto F1alpha by cultured aortic smooth muscle cells and stimulation of its formation in a coupled system with platelet lysates.

Prostaglandins. 1978 Mar;15(3):399-408

Thompson D, Eling T.

Mechanism of inhibition of prostaglandin H synthase by eugenol and other phenolic peroxidase substrates.

Mol Pharmacol. 1989 Nov;36(5):809-17.

Topper JN, Cai J, Falb D, Gimbrone MA Jr.

Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. Proc Natl Acad Sci U S A. 1996 Sep 17;93(19):10417-22.

Ullrich V, Zou MH, Bachschmid M.

New physiological and pathophysiological aspects on the thromboxane A(2)-prostacyclin regulatory system. Biochim Biophys Acta. 2001 May 31;1532(1-2):1-14. Review. .

Vane JR, Bakhle YS, Botting RM.

Cyclooxygenases 1 and 2. Annu Rev Pharmacol Toxicol. 1998;38:97-120. Review.

Wade ML, Voelkel NF, Fitzpatrick FA.

"Suicide" inactivation of prostaglandin I2 synthase: characterization of mechanism-based inactivation with isolated enzyme and endothelial cells.

Arch Biochem Biophys. 1995 Aug 20;321(2):453-8.

White HL, Tansik RL.

Effects of delta 9-tetrahydrocannabinol and cannabidiol on phospholipase and other enzymes regulating arachidonate metabolism.

Prostaglandins Med. 1980 Jun;4(6):409-17.